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V6

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/080,127 05/15/98 BLINKOVSKY A 5253.200-US

HM22/0830

EXAMINER

ANN QUINTERO
NOVO NORDISK OF NORTH AMERICA INC
405 LEXINGTON AVENUE
NEW YORK NY 10017

WEATHERSPOON, J

ART UNIT	PAPER NUMBER
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1645

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DATE MAILED:

08/30/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 09/080,127	Applicant(s) Blinkovsky et al
Examiner John K. Weatherspoon	Group Art Unit 1645

Responsive to communication(s) filed on Jun 3, 1999.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 46-89 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 46-89 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

1. Applicants amendment and election of the invention of Group I, i.e. claims 1-22, 27 and 44-45, with traverse in Paper No.9 dated 6/3/99 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). In view of applicants amendment and response, claims 46-89 drawn to the invention of elected Group I are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112 first paragraph

3. New grounds of rejection: In view of applicants amendment and addition of new claims 46-89, claims 46-89 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The originally filed specification and claims provide insufficient written description support for the new claimed recitation drawn to isolated polypeptides having aminopeptidase activity further having physicochemical properties of "an ability to hydrolyze a substrate containing Ala, Arg, Asn, ...or Val at its N-terminus" as recited in said new claims 46-89. In view that applicants have provided no reference or guidance for written description support from the original disclosure for this recitation in applicants

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amendment and response dated 6/3/99, applicants should point to the specification by page and line number where support for this language is drawn from and how it conveys the concept of the instant claim(s). Applicants do have sufficient written description for claim limitations as set forth in the originally filed claims, for example isolated polypeptides having aminopeptidase activity with "activity towards Xaa-para-nitroanilide" as set forth in originally filed claims.

4. New grounds of rejection: Claims 46-89 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claimed invention is drawn to isolated polypeptides having aminopeptidase activity and having "amino acid sequence which has at least 70%/80%/90%/95%/97% identity" with claimed SEQ ID Nos. However, one skilled in the art recognizes that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). In view that the claimed invention encompasses polypeptides with any number of amino acid substitutions, deletions and/or insertions, and in view that the above references demonstrate that even a single amino acid substitution or what

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appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein, e.g. biological activity with regard to claimed aminopeptidase activity, and in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives and fragments of polypeptides encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

The specification does not support the broad scope of the claims which encompass a multitude of analogs because the specification does not disclose the following: the general tolerance to modification and extent of such tolerance with regard to effects of amino acid substitutions, deletions and/or insertions on claimed aminopeptidase activity; specific positions which can be predictably modified; and the specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed polypeptides as set forth above in a manner reasonably correlated with the scope of the claims broadly including any number of deletions, additions and/or substitutions of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

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Claim Rejections - 35 USC § 112 second paragraph

5. In view of applicants amendment and addition of new claims 46-89, claims 46-89 are rejected under rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants broadly argue that the Clustal method “is well known in the art for determining sequence alignments” (page 8 of response). Applicant's arguments have been fully considered but are not deemed to be persuasive for the reasons set forth in the previous Office Action and the reasons discussed below. As set forth previously, the terms “70% identity”, “80% identity” and “90% identity”, “95% identity” and “97% identity” in said claims are relative terms which renders the claims indefinite since said terms in the specification (page 4) do not provide a standard for ascertaining the exact requisite degree of percent identity, and one skilled in the art would not be reasonably apprised of the scope of the invention. The specification (page 4) refers to the use of “the Clustal method with an “identity table” to measure sequence identity. However, the specification fails to clearly point out the parameters or properties of said “identity table”. Absent definite and clear parameters or description of said Clustal method identity table to determine percent identity of two sequences, use of said identity table could result in inconsistent assessment of sequence identity absent clear recitation of the parameters, and the metes and bounds of the sequences as instantly claimed can not be ascertained.

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6. New grounds of rejection: In view of applicants amendment, claim 64 and dependent claims thereof, i.e. claims 65-67, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims recite the limitation "the polypeptide of claim 1". There is insufficient antecedent basis for this limitation in the claims since claim 1 has been cancelled by applicants.

Claim Rejections - 35 USC § 102

7. In view of applicants amendment, new claims 46, 52, 56-63 and 69 are rejected under 35 U.S.C. 102(e) as being anticipated by Holm et al (U.S. Patent No. 5,821,104, filed March 19, 1997; cited in previous Office Action). Applicants argue (page 9 of response) that Holm et al do not disclose aminopeptidase "which sequentially removes one amino acid residue at a time from the N-terminus". Applicants arguments have been fully considered but are not deemed to be persuasive for the reasons set forth in the previous Office Action and the reasons discussed below. In particular, applicants arguments are not persuasive since applicants arguments are not commensurate in scope with the claimed invention, i.e. said claims do not claim aminopeptidase "which sequentially removes one amino acid residue at a time from the N-terminus". Further, applicants arguments that aminopeptidase is not tripeptidyl aminopeptidase are not commensurate in scope with the claimed invention, since claimed invention is drawn to any

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isolated polypeptides as claimed "having aminopeptidase activity". As set forth previously, Holm et al disclose isolated polypeptide having aminopeptidase activity wherein said polypeptide is encoded by a nucleic acid sequence which hybridizes with the nucleic acid sequence or a subsequence of SEQ ID NO:1 or its complementary strand and wherein said polypeptide is obtained from an *Aspergillus oryzae* strain (see entire reference). Holm et al also disclose a polypeptide comprising a fragment of the sequence of instant SEQ ID NO:2 and a method for producing said polypeptide comprising recovering said polypeptide from said *Aspergillus* strain. In view of said disclosure the limitations of said claims are anticipated by the prior art.

Status of Claims

8. No claim is allowed.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology center 1600, Group 1645 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1645 is (703) 308-4242.

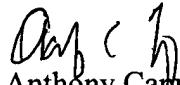
Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Weatherspoon, Ph.D. whose telephone number is (703) 305-0557.

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The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached at (703) 308-3995.

John Weatherspoon, Ph.D.

August 18, 1999


Anthony Caputa, Ph.D.

Supervisory Primary Examiner

Group 1645